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Curcumin loaded nanoparticles: Breaking barriers to brain delivery

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ABSTRACT

The blood-brain barrier (BBB) is a semipermeable barrier that protects the brain from potential pathogens. Despite its protective nature, BBB prevents the passage of any medication into the brain, except for those with a low molecular weight (below 500 Da) and lipophilic compounds. In this research, we developed PEGylated curcumin loaded mesoporous silica nanoparticles (P/CRM@MSNs) that were fabricated to target the brain by either bypassing or crossing the BBB intranasally (in) and intravenously (iv), respectively. Various techniques were employed to characterize the P/CRM@MSNs. In vivo experiments demonstrated that intranasal administration of P/CRM@MSNs improved cellular uptake and reduced clearance from brain tissues, showing a three-fold increase compared to intravenous administration at one-hour post-injection. Pharmacokinetic analysis revealed a higher AUC_(0-1h) value (324 ± 75 ng. h/ml; $P < 0.05$) following intranasal administration than intravenous administration (195 ± 55 ng. h/ml). Intranasal administration of P/CRM@MSNs significantly reduced drug clearance from the brain (0.2 ± 0.05 ml/h) compared to intravenous administration (0.4 ± 0.06 ml/h). These findings suggest that P/CRM@MSNs could be a promising nanocarrier system for treating brain disorders.

Keywords: Curcumin, Mesoporous silica nanoparticles, Blood-brain barrier, Intranasal, Intravenous

1. INTRODUCTION

The BBB is a complex protective barrier that restricts the entrance of any pathogen into the brain (Pardridge, 2007). Curcumin is a lipophilic compound with many pharmacological activities, especially in the brain, including free radical scavenging, protein accumulation inhibiting, and hemostasis regulating in the brain (Bhat et al., 2019). However, the presence of BBB hinders the outstanding properties of this hydrophobic molecule in the brain and its entrance into the brain (Siviero et al., 2015). The brain uptake of curcumin can be enhanced by encapsulating this polyphenolic compound inside the nanoparticles (Chen et al., 2020). Currently, curcumin delivery through inorganic nanocarriers is the

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preferred method. Among them are mesoporous silica-nanoparticles, characterized by their high surface area and large pore volume, allowing a high drug payload (Maleki-Dizaj et al., 2022).

According to a literature survey, mesoporous silica nanoparticles have been used little in the brain drug delivery field. The intranasal instillation of hydrogel@curcumin loaded mesoporous silica nanoparticles into the brain to treat Alzheimer's disease could lessen Aβ aggregations in the brain (Ribeiro et al., 2022). Another study by Taebnia et al., (2016) reported that curcumin loaded with amine-mesoporous silica nanoparticles could suppress the formation of α-synuclein and its cytotoxic effect related to Parkinson's disease. A survey by Huo et al., (2019) showed that the injection of curcumin-encapsulated PLGA selenium nanocomposite improves the therapeutic efficacy of curcumin through its binding with the formed amyloid β-plaques in the brain.

This research has developed PEGylated curcumin loaded mesoporous silica nanoparticles (P/CRM@MSNs) with distinct physicochemical properties. In an in vivo study, P/CRM@MSNs were delivered intranasally (in) and intravenously (iv) in mice groups bypassing or crossing the BBB, respectively. The results showed that the intranasal injection of P/CRM@MSNs delivered the highest amount over all the studied periods compared to iv one. The calculated pharmacokinetic parameters were enhanced significantly for those intranasally routed over that intravenously.

2. MATERIALS AND METHODS

Materials

Curcumin (CRM), with a concentration of less than 85%, and phosphate-buffered saline in tablet form were procured from Sigma Aldrich. The mesoporous silica nanoparticles (MSNs), prepared beforehand, were generously provided by Cairo University.

Physicochemical characterization of P/CRM@MSNs

The morphology and size of the prepared mesoporous silica nanoparticles (MSNs) were analyzed using a transmission electron microscope (TEM, FEI, Netherlands) operating at a voltage of 200 kV. The surface charge was measured using a Malvern Zeta sizer Nano-ZS (Malvern Panalytical Ltd., UK). The thermal properties of CRM@MSNs were assessed using differential scanning calorimetry (DSC, SETARAM Instrumentation KEP TECHNOLOGIES, Switzerland), with a heating rate set at 2 ℃/*min*.

Animals

Female Swiss mice (N = 12) were managed in compliance with the approved protocol from the Animal Care and Use Committee office's authorized protocol number (ACUC-21-03-14). The mice were maintained under 64-72 % humidity and a temperature of 20 ℃. All animals have access to water and a regular diet.

Brain uptake of P/CRM@MSNs

In the brain uptake study, the experiment was carried out on four groups of mice. Two groups (n = 3) of mice were separately injected with P/CRM@MSNs intranasally (in) and intravenously (iv), each with a curcumin concentration of 0.31 mg/ml. The other two corresponding control groups were also separately injected with 9 % saline intranasally and intravenously. After 0.25 h and 1 h of P/CRM@MSNs injection, the mice were fully anesthetized, and the brain samples were removed, washed three times with saline, and homogenized (Homogenizer, KINEMATICA GmbH PCU, Canada). The homogenized brains were centrifuged (Sigma, Germany) for 15 min at 5 ℃. The samples were stored at – 80 ℃ until analysis.

Fluorometric measurements

The concentration of curcumin from P/CRM@MSNs in all the brain homogenate samples was determined at a wavelength of 425 nm.

Statistical analysis

All data and group differences were analyzed using a T-test with a significance level set at $P < 0.05$.

3. RESULTS AND DISCUSSION

P/CRM@MSNs characterization

The TEM image of the blank MSNs revealed a material with a porous structure and a smooth spherical surface (Figure 1). The TEM image exhibited well-monodispersed nanoparticles. The TEM image displayed that the MSNs had a size of 137 ± 19 nm. It is believed that the size of the nanoparticles under 200 nm can easily penetrate the BBB (Chen et al., 2019). The Zeta potential measurement of P/CRM@MSNs was - 14.3 ± 2 mV. Our result is consistent with the previous findings by Ma et al., (2014) which indicated a negative zeta potential after curcumin-loading. In the DSC measurement, the endothermic curve of CRM@MSNs exhibited a characteristic peak at 103 ℃, which confirmed the successful conjugation of curcumin molecules into the pores of mesoporous silica nanoparticles. This result is in line with the previous study (Chen et al., 2018).

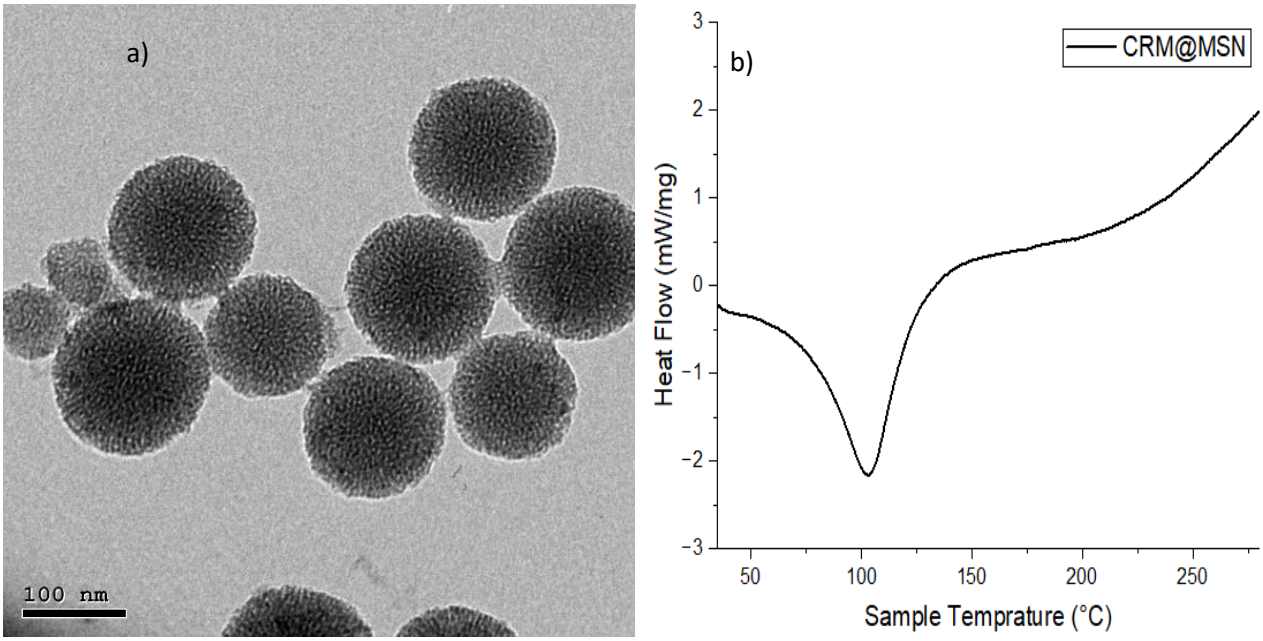

Figure 1 a) Transmission Electron Microscopy (TEM) image of blank Mesoporous Silica Nanoparticles (MSNs), and b) Differential Scanning Calorimetry (DSC) spectrum of curcumin-loaded MSNs (CRM@MSNs).

P/CRM@MSNs uptake study

Figure 2 shows the delivery of P/CUM@MSNs into the brain, bypassing or crossing the BBB through the intranasal or intravenous administration routes, respectively, through two different time intervals (0.25 and 1 h). The accumulation of P/CRM@MSNs was exhibited early at 0.25 h with concentrations of 334 ± 33 and 115 ± 7 ng/ml for both in and iv, respectively. At one hour following intranasal injection, the amount of the injected P/CRM@MSNs has significantly increased (690 ng/ml; $P < 0.01$) in the brain tissues. In contrast, little increase (214 ± 8 ng/ml) has been noticed in the administrated P/CRM@MSNs in the brain homogenate post iv. The above results showed a twofold increase following intranasal comparison to intravenous. Notably, the concentration of P/CRM@MSNs was observed with significant amounts of injection compared to iv ($P < 0.01$).

The above outcomes revealed that the intranasal route increased the amount of curcumin in the brain tissues and prevented the phagocytosis of nanoparticles by macrophage. Furthermore, the conjugation of PEG to the surface of curcumin loaded nanoparticles enhances the transportation of the drug through BBB (Hu et al., 2017; Wang et al., 2018). Additionally, the direct nose-to-brain delivery leads to maximum accumulation amounts of P/CRM@MSNs in the brain tissues within one hour post intranasal instillation (Yokel, 2020). Moreover, as mentioned previously, the results demonstrated that the intranasal injection of P/CRM@MSNs considerably increased the distribution of curcumin in the brain tissues through the olfactory pathway. Thus, the transportation of the drug is confirmed by a direct route via 5 mm olfactory bulb length (Yokel, 2020).

In contrast, the quantity of the drug in brain tissues is reduced when P/CRM@MSNs are administered via intravenous (iv) injection. This reduction is due to the drug's dilution in the systemic circulation following administration. Furthermore, the minimal presence of P/CRM@MSNs in the brain post-iv injection can be attributed to its disintegration in the physiological environment (Shah et al., 2016). Furthermore, the hydrophilicity of the PEG coating layer could prolong the circulation time, reducing the reached amounts in the brain tissues (Calvo et al., 2001). Chen et al., (2013) developed curcumin-loaded thermosensitive poloxamer hydrogel. The intranasal (in) and intravenous (iv) administration of the prepared nanoparticles demonstrated a general increment of curcumin concentration in brain regions following in compared to iv post 6 min of injection.

Another study by Shinde and Devarajan, (2017), prepared curcumin loaded Campul microemulsion. The intranasal delivery of CUR Campul ME exhibited higher pharmacokinetic parameters of area under the curve (4450.30 ± 43.87 ng. h/mL) over that following intravenous (1931.76 ± 42.71 ng. h/ml), showing a 2-fold increase compared to iv. The calculated elimination rate constant of intranasal administration of CUR Campul ME was K_el = 0.0440 ± 0.0032 h^-1, which is slower than that iv (K_el = 0.0785 ± 0.0053 h^-1). Additionally, the injection of CUR Campul ME intranasally enhanced the half lifetime (T_1/2) significantly to 16.64 ± 1.24 h compared to that intravenous (14.42 ± 0.97 h). The above results demonstrated that the intranasal injection of curcumin loaded nanocarrier significantly increased the reaching amount in the brain and enhanced the pharmacokinetic parameters over that injected intravenously (Shinde and Devarajan, 2017). This finding aligns with our results.

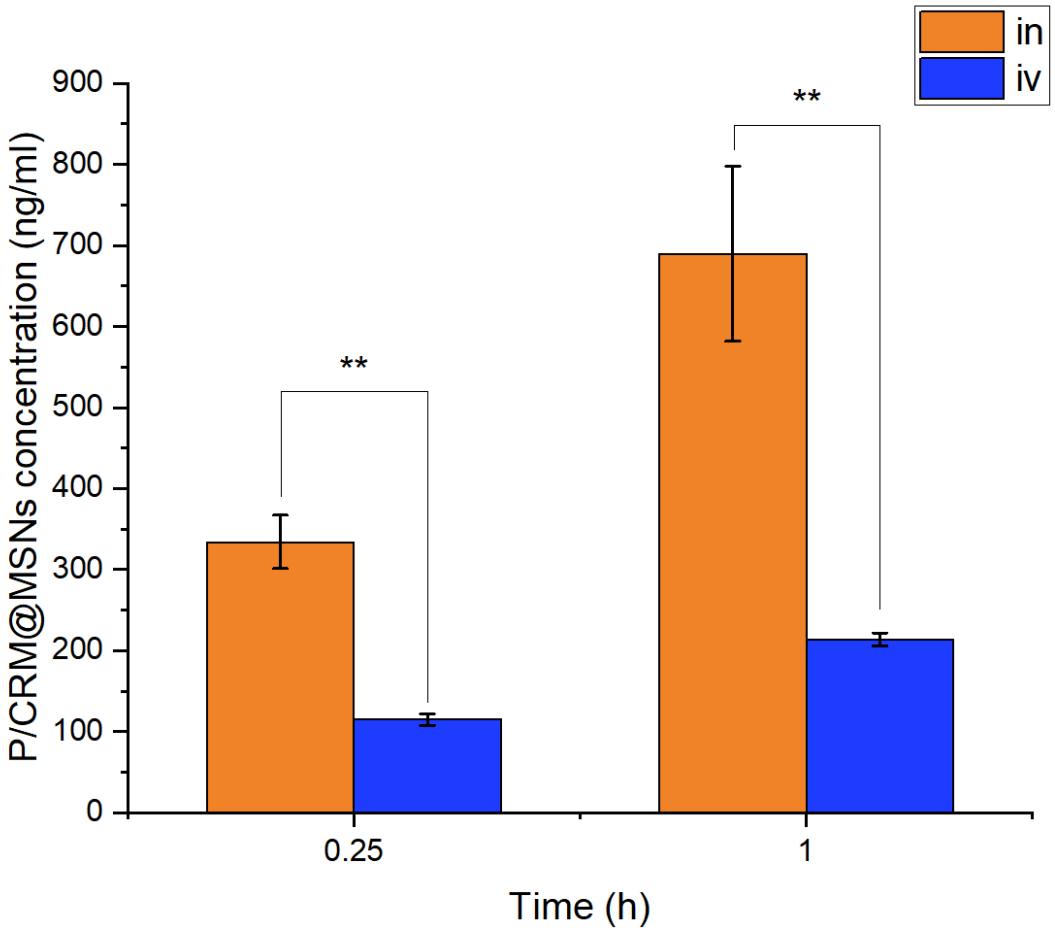

Figure 2 Concentration of P/CRM@MSNs in brain homogenate following intranasal (in) and intravenous (iv) administration in distinct mouse groups (n=3). Data are represented as mean ± SD. **P < 0.01.

Pharmacokinetic parameters in the brain

Based on the fluorometric measurements of the administrated P/CRM@MSNs in the brain through in and iv routes, some pharmacokinetic parameters of elimination rate constant (K), distribution volume (VD), half lifetime (T_1/2), clearance (Cl), mean residence time (MRT), and area under the curve from 0 h to 1 h AUC_(0-1h) were calculated. Table 1 displayed an area under the curve following in administration (324 ± 75, P<0.05) higher than that iv (195 ± 55), showing a 1.7-fold increase. The use of the direct intranasal route causes the path from the nose to the brain to bypass the BBB (Yokel, 2020). The calculated elimination rate constant (K) following both routes in and iv was nearly in the same range, 0.95 ± 0.19 h^-1 and 0.83 ± 0.05 h^-1. Moreover, the administration of the P/CRM@MSNs intranasally slowed its clearance from the brain.

In contrast, administering the P/CRM@MSNs through systematic circulation to the brain increased its clearance from the brain and decreased its amounts in brain tissues, delaying its delivery to the brain. The calculated half-lifetime was 0.7 ± 0.12 h and 0.8 ± 0.05 h post in and iv administration routes, respectively. All the calculated pharmacokinetic parameters confirmed the priority of administering the drugs to the brain via the intranasal route over the intravenous one. The intranasal route transports the injected drug directly from the nose to the brain, bypassing the BBB via a 5 mm length of the olfactory bulb. Meanwhile, using the intravenous route to administrate P/CRM@MSNs slows the injected drug's reaching the brain and prolongs its transport through systematic circulation. Surprisingly, both routes of administrations in and iv successfully delivered P/CRM@MSNs bypassing or crossing the BBB into the brain.

Table 1 Pharmacokinetic parameters of P/CRM@MSNs in brain tissues post both in and iv administration routes in mice groups (n = 3). Data are represented as mean ± SD.

Pharmacokinetic Parameters in the Brain	**Route of Administration**	
	in	**iv**
AUC_(0-1h) (ng. h/ml)	324 ± 75*	195 ± 55
K (h^-1)	0.95 ± 0.19	0.83 ± 0.05
Cl (mL/h)	0.2 ± 0.05*	0.4 ± 0.06
T_1/2 (h)	0.7 ± 0.12	0.8 ± 0.05

*Indicates p<0.05 compared to iv group.

4. CONCLUSION

The suggested P/CRM@MSNs could significantly deliver curcumin to the brain via different administration routes: Intranasal and intravenous. Thus, the prepared P/CRM@MSNs under the size of 200 nm can overcome the BBB's obstacles. The administration of P/CRM@MSNs with distinct physicochemical properties via the intranasal route doubled the drug concentration in the brain tissues compared to the intravenous route. The corresponding pharmacokinetic parameters significantly enhanced post-intranasal administration compared to that post iv. The findings recommended prolonging the period of administration via both routes.

Author's Contributions

Balsam F Sofi: Responsible for the design of the methodology, the creation and characterization of nanoparticles, conducting in vivo studies, analyzing and curating data, drafting the original manuscript, and providing technical administration.
Reem Darwesh: Responsible for reviewing and editing the manuscript.
Nihal S Elbialy: Responsible for overseeing the work, conceptualizing the study, and approving the final publication.

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Ethical approval

The study was approved by the Animal Care and Use Committee office's authorized protocol number (ACUC-21-03-14).

Informed Consent

Not applicable

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This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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